Anabolic-androgenic steroids and cardiovascular risk

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Abstract

Objective: Anabolic-androgenic steroids (AAS) represents a group of synthetic testosterone derivatives that play an important role in clinical treatment. These drugs are widely abused among the general public to increase lean weight and improve athletic performance. It has been reported that AAS use can produce many adverse effects, especially the occurrence of cardiovascular risk. Although there are many related studies, there has been no consensus on AAS use and cardiovascular risk. The present study was to review the effect of AAS on the cardiovascular system.

Data sources: The data in this review were obtained from articles included in PubMed and the National Center for Biotechnology Information database.

Study selection: Original articles, case reports, and systematic reviews about AAS were selected for the article.

Results: The use/abuse of AAS is correlated with higher cardiovascular risks, and many AAS users/abusers had cardiovascular diseases. However, there are many confounding factors in the studies that explored the causality between AAS intake and disease development, and additional studies are required to determine AAS toxicity.

Conclusion: AAS produces toxic effects on the cardiovascular system, and it is necessary to ensure that more people know this about AAS, including medical personnel.

Keywords: Anabolic-androgenic steroid; Cardiovascular risk; Toxicity effects

Introduction

Anabolic-androgenic steroids (AAS), including testosterone and its numerous derivatives that have been modified to improve anabolism, are usually used to boost protein synthesis, muscle growth, and erythropoiesis.[1] Common preparations are Nandrolone, Stanozolol (STZ), Oxandrolone, Methandrostenolone, and Trenbolone, and some are parenteral or oral formulations.[2]

Since the 1940s, these drugs have been used in rehabilitation from burns, trauma, and surgery.[3] Following in-depth research, AAS began to be used to treat diseases that are associated with aging such as physiological or pathological hypogonadism and osteoporosis.[4,5] Moreover, high doses of AAS can treat cachexia, which is caused by human immunodeficiency virus and cancer, by promoting protein synthesis and maintaining and increasing lean mass.[6,7] Many prospective randomized studies have shown that androgens can be used to treat leukemia by stimulating bone marrow proliferation and hematopoiesis.[8] Bar *et al*[9] found that androgen therapy resulted in telomerase up-regulation and improvement in the blood count. Thus, it makes sense to prolong the life-span of these mice by designing a mouse model of aplastic anemia that was induced by short telomeres in the bone marrow compartment. Additionally, androgens can promote growth by stimulating growth hormone synthesis to treat some diseases that result in short stature and stunted development, such as Turners syndrome.[10] Ongoing progress in medical research has shown that AAS can be used in the treatment of breast cancer.[11] Appropriate doses of testosterone (T) or T combined with anastrozole (A) in women with hormone deficiency caused a reduced incidence of breast cancer, and T + A implants placed in breast tissue surrounding malignant tumors significantly reduced breast tumor size, indicating that T has a direct anti-proliferative and protective effect that was delivered by the sub-cutaneous implants for breast cancer treatment. Many medical studies on AAS have shown that AAS play an important role in the treatment of an increasing number of diseases.

However, in the 1950s, AAS started to be used by elite athletes as a stimulant to enhance athletic performance and increase muscle mass.[2] Use/abuse of AAS occurs worldwide, and the most common motives for using

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AAS are increased athletic performance, building muscles, improved physical appearance, strengthened libido, and an enhanced self-confidence.[12] The adverse effects of AAS abuse have been gradually recognized, and using AAS is associated with non-negligible toxic effects on the body. Long-term AAS use can induce abnormal endogenous hormone secretion, producing reversible or irreversible damage. The most common side effect of AAS is increased secretion of oil from sebaceous glands, which causes dermatological diseases such as acne vulgaris, androgenic alopecia, and hypertrichosis.[13] AAS can also induce some sex problems, such as testicular atrophy, impotence, azoospermia, and infertility in men.[14,15] In women, AAS abuse can produce voice changes, amenorrhea, uterine atrophy, and clitoral enlargement.[15] In athletes, AAS abusers are at a significantly increased risk of tendon ruptures, which is a crushing blow for the athlete's career.[16] Additionally, long-term AAS users are prone to psychobehavioral disorders such as headache, irritability, depression, and AAS dependence syndrome,[17] leading to violence and suicide in some cases.[13] An excessive oral AAS burden is metabolized by the hepatorenal system, which aggravates hepatorenal damage, and it could also cause liver or kidney diseases, such as coagulation dysfunction, liver fibrosis, renal hypertrophy, and renal failure.[18,19] AAS abuse also increases the cardiovascular risk and seriously threatens the safety of its users.[13,20]

Effects of AAS on the Cardiovascular System

Cardiovascular diseases are considered to be the largest threat to human life, and it is a main public health issue worldwide.[21,22] Diseases that involve the heart and blood vessels include coronary artery disease (CAD), hypertension, cardiac arrhythmia, cardiomyopathy, and thromboembolism. The underlying pathogenic mechanisms vary depending on the type of disease. However, the cardiovascular system in most AAS abusers is always unhealthy, and the cardiovascular lesions in AAS abusers vary because of individual differences, presenting diverse signs and symptoms.

Vascular calcification

One study addressed the hypothesis of exogenous androgen-induced vascular calcification. Immunohistochemical analysis showed expression of the androgen receptor (AR) in the calcified tissue of human femoral artery and in calcified human valves, and *in vitro* studies revealed that 9 days of treatments with testosterone or dihydrotestosterone resulted in increased calcification of phosphate-induced mouse vascular smooth muscle cells.[23] These experimental data suggest that androgens increase the degree of vascular calcification through binding to AR, then directly inducing cell damage, resulting in loss of tissue elasticity and ultimately fibrotic hyperplasia.[24]

Atherosclerosis

Atherosclerosis is a disease in which the artery narrows because of plaque formation, and lipid metabolism disorder is the pathological basis of atherosclerosis. Samieinasab *et al*[25] found that AAS can induce lipid metabolism disorder, which leads to decreased high-density lipoprotein (HDL) and increased low-density lipoprotein (LDL) levels, which increase the risk of CAD and cerebrovascular disease.[26] It has been shown that physical exercise increases the HDL level and has a remarkable effect on the reduction of LDL and triglyceride levels, thereby reducing the harmful effects of AAS in the body.[27] Lipoprotein levels will return to their normal range after AAS is discontinued for weeks to months.[28] Additionally, Peoples *et al*[29] reported that long-term AAS abuse leads to a continuous increase in homocysteine levels in the blood, resulting in hyperhomocysteinemia, which is a risk factor for coronary atherosclerosis, and this increases the incidence of CAD.

Thromboembolism

AAS can directly affect the coagulation/fibrinolysis system,[30] and abusers have an increased risk of arterial and intra-cardiac embolism and a higher incidence of deep vein thrombosis and pulmonary embolism.[31] These drugs enhance platelet generation and aggregation, which expand the range of thrombus embolism[32] and promote the generation of thrombin[33] and thromboxane A2 (TXA2), which inhibit the production of prostacyclin (prostaglandin I2, an inhibitor of platelet aggregation) and results in hypercoagulability.[26,34] Additionally, testosterone directly regulates TXA2 receptor density on platelets and vascular cells, thus affecting the coagulation/fibrinolysis function.[35] However, prospective studies are required to clarify whether this pathological state increases the thrombotic risk in AAS abusers even after cessation.

Hypertension

The link between AAS and blood pressure (BP) is unclear. A correlation between AAS use and higher BP has been found in some studies,[26,36] whereas other studies have shown no association.[37-39] Junior *et al*[40] found that, compared with the pre-exercise baseline, there was no significant decrease in arterial pressure from 30 to 60 min after exercise in AAS users, indicating that AAS inhibited post-exercise hypotension. The effect of AAS use/abuse on BP may persist for long periods, and some studies have reported a persistent BP elevation for 5 to 12 months after cessation.[41] When reversible hypertension is observed, it may follow water–sodium retention in the kidney that is induced by AAS, which results in an increase in blood volume and BP.[42] If such hypertension is irreversible, AAS-induced atherosclerosis will likely be the main cause. Because the analysis is complicated by many factors, such as dose and duration of AAS use, additional studies are necessary to further reveal the link between AAS and BP.

Coronary spasm

A physiological dose of AAS directly binds to the AR on the arteries, which promotes the release of nitric oxide to inhibit vascular smooth muscle tension by activating the smooth muscle ion channels such as L-type voltage-gated Ca^{2+} channels, voltage-gated K^+ channel, and Ca^{2+}-activated K^+ channels, which induce vasodilatation.[43,44] However, supraphysiological doses cause coronary spasm. Sonmez

et al[45] reported a clinical case of a 32-year-old male who had severe chest pain and was admitted to the local hospital. He had been taking AAS (200 mg weekly) for 3 years for bodybuilding. Medical examination showed that his cardiac markers were elevated remarkably, but his electrocardiogram (ECG) did not show ST elevation or depression in each derivation, only showing peaked T waves. The diagnostic coronary angiogram showed completely normal states in both the right and left coronary artery systems. Ferrer *et al*[46] showed that constriction of the thoracic aorta was correlated with lower concentrations of arterial endothelial cyclic guanosine monophosphate, which is inhibited by androgens. However, Liu *et al*[47] reported that patients with CAD had a decreased AR expression in the coronary arteries and they were more likely to have coronary spasm because of the favorable effect of AR. Therefore, we hypothesize that the vasospasm effect may be enhanced in AAS abusers with CAD, even inducing myocardial infarction. The sudden vasoconstriction causes detachment of atherosclerotic plaques and thrombosis forms, which obstructs coronary artery lumens, resulting in ischemic myocardial necrosis.

Myocardial apoptosis

AAS is associated with myocardial apoptosis.[48] In an animal model, ventricular myocytes were isolated from adult male rabbits and treated *in vitro* for 20 h using different doses of STZ, *Testosterone Enanthate* (TE), and *Testosterone* (T) (0.1, 1, 10, and 100 μmol/L). These results showed, for the first time, that AASs induce significant myocardial apoptosis in a dose-dependent manner.[49] Similar apoptosis in myocardial cells was observed by Fanton *et al*[50] after norethandrolone therapy. Most of the histopathological examination of hearts from treated rabbits showed that these myocardial lesions were similar to adrenergic or toxic myocarditis, and caspase-3 activity was increased in the hearts of treated animals, indicating that apoptosis was involved in the process of norethandrolone-induced cardiac lesions. Hassan *et al*[51] designed a controlled experiment using rats to explore the effects of AAS on apoptosis and histology of cardiac muscle. The results showed that cardiac caspase-3 activity was significantly elevated in rats treated with nandrolone decanoate, and histological examination showed apoptosis and hypertrophy of cardiac myocytes. Additionally, a clinical case report showed that AAS abusers with normal coronary arteries were diagnosed with left ventricular hypertrophy with myocardial scarring.[52] It was also suggested that AAS induces myocardial apoptosis. These studies indicated that AAS had a pro-apoptotic effect on cardiac myocytes. Vicencio *et al*[53] suggested that androgens promoted Ca^{2+} influx and Ca^{2+} mobilization in the sarcoplasmic reticulum to increase mitochondrial permeability, which led to the release of apoptosis factors, such as cytochrome C, apoptosis-inducing factor, and caspase, resulting in apoptosis.

Cardiac hypertrophy

Some controlled experiments that examined the hearts of AAS users and non-users using standard Doppler echocardiography or cardiac magnetic resonance imaging, have shown pathological cardiac hypertrophy in AAS users.[38,54] AAS-induced cardiac hypertrophy should be distinguished from physiological hypertrophy, which causes a reduction in ventricular compliance and degradation of cardiac inotropes.[55-57] Liu *et al*[58] have found that 5α-reductase, aromatase, and AR expression levels were significantly elevated in hypertrophic hearts in both humans and mice, and it was suggested that AAS increased protein synthesis,[59] which was a vital stage in the process of cardiac growth[60] in myocardial cells by activating intra-cellular AR. Additionally, AASs can strongly stimulate collagen production and myocardial fibroblastic growth.[61] Many patients with cardiac hypertrophy are professional athletes who have been using AAS for a long time, especially bodybuilders and powerlifters,[20] and high-intensity training and AAS have a cumulative effect on cardiac hypertrophy, causing cardiac dysfunction and even heart failure.[55]

Dilated cardiomyopathy

Some case reports suggested that dilated cardiomyopathy in bodybuilders was directly related to AAS abuse.[32,62,63] However, further studies suggested that dilated cardiomyopathy is mainly related to an individual's genetic background.[64,65] Dilated cardiomyopathy is an autosomal dominant disease in most clinical cases, and it rarely shows autosomal recessive or X chromosome inheritance. Some dilated cardiomyopathy cases may be caused by infection or immune and environmental factors.[66]

Arrhythmia

AAS can induce abnormal electrical activity of the heart in abusers, and ECGs often show irregular electrical activity during physical exertion, such as QRS-wave delay, ventricular fibrillation (VF), supraventricular, and ventricular ectopic beat.[26] Barbosa *et al*[67] showed that long-term use of a supraphysiological AAS dose would induce cardiac autonomic disorders, suggesting that AASs induce autonomic nervous dysfunction by affecting a variety of neurotransmitter systems, such as the dopaminergic system, the 5-hydroxytryptophan system, and the GABA system.[68,69] Ghorbani *et al*[70] have reported in a controlled experiment that the combination of exercise and nandrolone remarkably increased the incidence of VF and reduced the VF latency. Medei *et al*[71] investigated the mechanism of ventricular repolarization with AAS treatment at the cellular, ionic, and molecular levels, and they found that supraphysiological doses of AAS caused morphological remodeling in bilateral ventricles as well as electrical remodeling, especially in the left ventricle, and it was suggested that a supraphysiological dose of AAS induced a disorder of electrical activity, resulting in cardiac autonomic dysfunction.

Sudden cardiac arrest

Clinical cases have demonstrated that AAS abuse is associated with sudden cardiac arrest,[72,73] but the mechanism of the sudden cardiac arrest remains unknown. On the one hand, most AAS abusers' death from sudden cardiac arrest was observed as cardiomyopathy, such as

cardiac hypertrophy, ventricle dilatation, and myocardial fibrosis, during an autopsy.[74-76] On the other hand, many AAS abusers use a variety of AASs, and combine multiple drugs to enhance the anabolic stacking effects. Body-builders use oral and injection AASs, and also supra-physiological doses of recombinant human growth hormone, insulin, and thyroid hormones (T3, mainly), which enhance muscle growth, nutrient absorption, and metabolism, respectively,[77-79] and diuretics are used to minimize sub-cutaneous water to obtain a "hard" look.[80] The combination of these drugs may cause a lethal effect, but more studies are needed to support the suggestion. AAS can quickly inhibit the re-uptake of catecholamines into extra-neuronal tissue, and consequently increase the concentration of catecholamines at the receptor sites.[31] Therefore, the combination of AASs and physical exercise over-stimulates the sympathetic nervous system to induce a temporary functional disorder of the sympathetic axon terminals, which increases the susceptibility to VF, resulting in sudden cardiac death.[81] Thus, we guess that professional athletes with a history of long-term AAS use are more likely to experience sudden death.

Discussion

AAS has a protective effect on the cardiovascular system in the physiological dose range. However, supraphysiological AAS doses produce toxicity in the cardiovascular system, which significantly increases the cardiovascular risk [Figure 1].

The mechanism of AAS toxicity has not been fully elucidated. Studies demonstrated that there were two main mechanisms [Figure 2], one of which is AAS gene

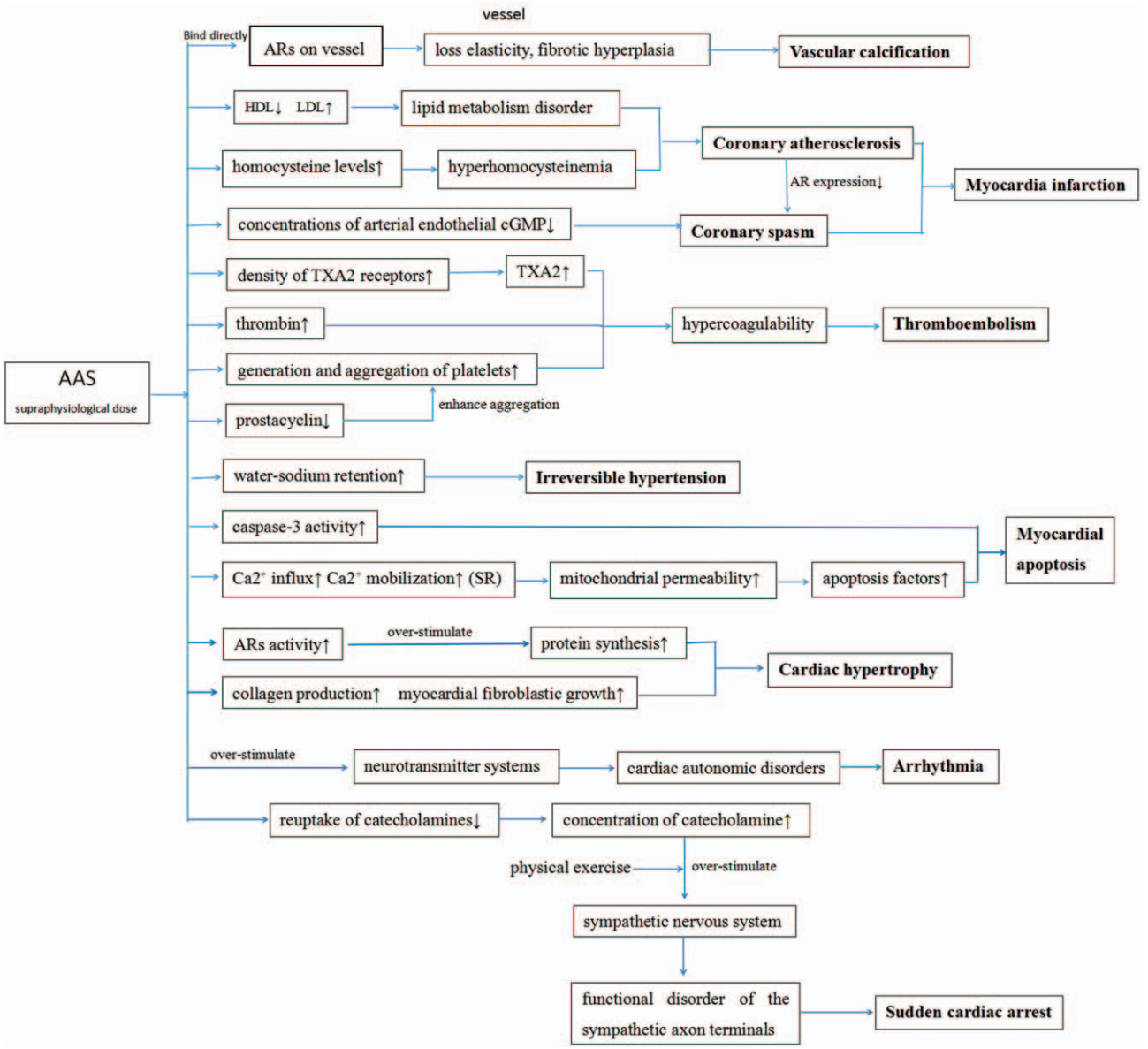

Figure 1: The toxicity effects of AAS on the cardiovascular system. ↑: increase/enhance; ↓: decrease/inhibit. AAS: Anabolic-androgenic steroids; AR: Androgen receptor; cGMP: Cyclic guanosine monophosphate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SR: Sarcoplasmic reticulum; TXA2: Thromboxane A2.

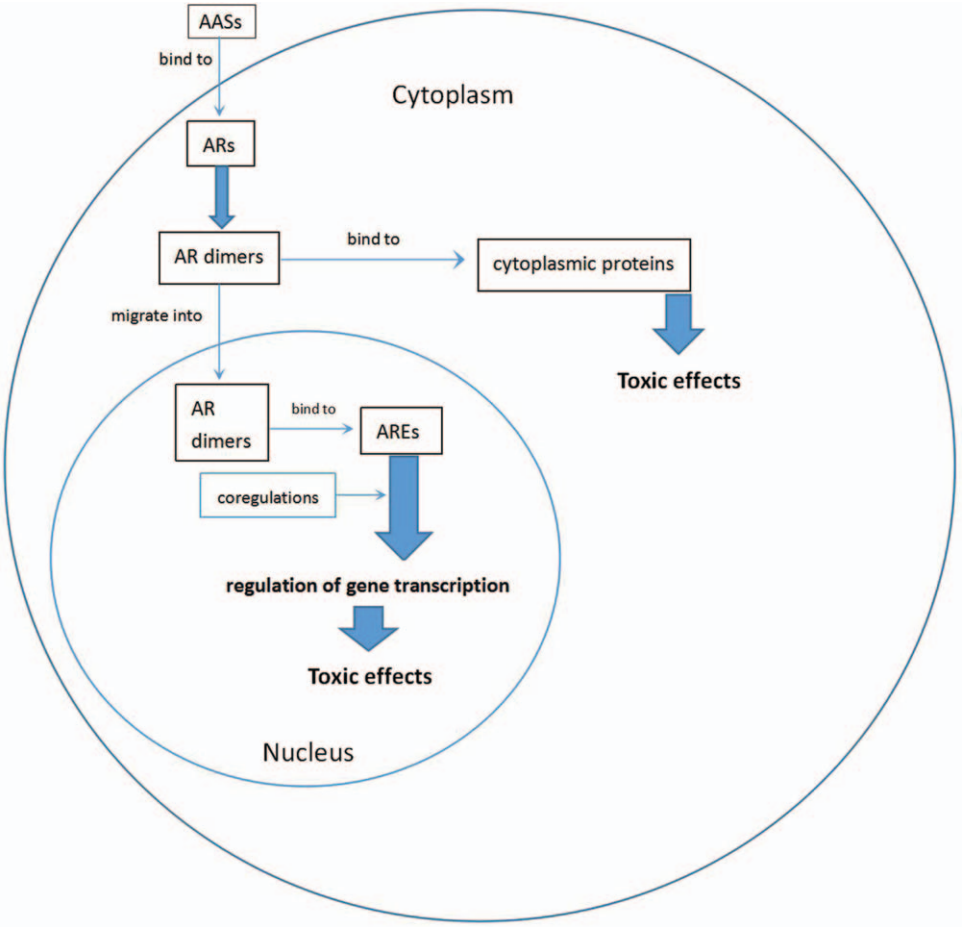

Figure 2: The two main signaling pathways of AAS toxicity. AAS: Anabolic-androgenic steroids; AR: Androgen receptor; ARE: Androgen reactive element.

regulation where AASs or their metabolites bind to ARs, which leads to a conformational change of these receptors. AR dimers are then transported from the cytoplasm into the nucleus where the dimers bind to androgen reactive elements in DNA, thereby regulating gene transcription in cooperation with activation (or inactivation) of co-regulations, which results in toxic effects.[82] Another non-gene regulatory mechanism (mainly in skeletal muscle cells and prostate cancer cells) is that AR dimers bind to cytoplasmic proteins through a variety of signaling pathways that directly induce toxicity without gene transcription pathways.[82,83] The degree of AAS toxicity is related to a variety of factors such as dose, cycle, and individual differences. Through medical examinations, people taking AASs for a period of time or even a few years may not show any abnormal index results.

There are some difficulties in studying AAS toxicity in the cardiovascular system. First, a general limitation of these studies results from the information about AAS doses and cycles of use/abuse, which is self-reported, and it is difficult to objectively assess the exact data.[84] Additionally, because of the stacking effect from polydrug abuse, it is difficult to assess the toxic effects of AAS.[85] These studies only demonstrated AAS-related cardiovascular lesions by observing the morphological and functional differences between the experimental group and the control group, which did not clarify the causality between AAS intake and disease development.[55] However, it is unethical to design control experiments in humans because long-term administration of high AAS doses in the experimental group would be life-threatening.[72,73] Although the mechanism and toxicity of AAS can be explored using animal model experiments, there are differences between humans and animals, and the results may show different effects and metabolic pathways for AASs.

The general therapy for AAS toxicity is drug cessation.[86] However, most case reports have not shown whether AAS was discontinued immediately or if the dose was reduced gradually.[45,87,88] Immediate discontinuation of high-dose AASs after long-term can lead to the withdrawal responses, including mood disorders (depression), anorexia, decreased libido, insomnia, fatigue, headache, and the desire to take more steroids.[86] These withdrawal reactions would increase the seriousness of the illness in AAS users. Therefore, we suggest that causative therapy combined with gradual reduction of AAS doses is a more sensible scheme to treat users/abusers.

Currently, few people really understand the effects of AAS on health,[89] but the recreational use of such drugs is becoming increasingly popular.[3] The largest group of AAS users are "average people who just want to get

stronger as soon as possible," and most AAS users had a positive attitude toward the effects of AAS; they felt more confident after becoming stronger and considered that moderate use of AASs was harmless for the body.[12] Recently, AAS abuse has become more widespread in Western countries and is less widespread in Africa and Asia,[90] but bodybuilding has become increasingly popular in China. Thus, AAS abuse will become a potential public health concern because of the limited knowledge and awareness of recreational bodybuilders about AAS toxicity. Therefore, it is necessary to increase awareness about the harm caused by AAS, especially for those who use AAS recreationally. For AAS users/abusers, stronger is a temporary illusion, which results in somatic damage.

The knowledge of AAS users about the combination of various drugs becomes extensive after using such drugs for a period of time, even resulting in the comment "I know more than doctors."[21] Unfortunately, the comment reveals the truth that doctors and other medical professionals have a limited knowledge of AAS, which causes a high level of distrust from AAS users toward clinicians.[91] Therefore, it has become important for clinicians better understand AAS. Only by knowing more will the patients trust the diagnosis and undergo treatments.

Conclusion

AASs can increase protein synthesis, muscle growth, and erythropoiesis, and they also play key roles in clinical treatment. However, abuse of AAS has a toxic effect on the cardiovascular system, which significantly increases the incidence of cardiovascular diseases such as coronary atherosclerosis, hypertension, myocardial necrosis, cardiac hypertrophy, thromboembolism, and arrhythmia. Thus, it is necessary to increase the awareness of AAS toxicity in the general population. If a person insists on using AASs, they should seek professional advice from experts.

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Conflicts of interest

None.

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